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Subjective embodiment during the rubber hand illusion predicts severity of premonitory sensations and tics in Tourette Syndrome

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Abstract

In Tourette Syndrome, the expression of tics and commonly preceding premonitory sensations is associated with perturbed subjective feelings of self-control and agency. We compared responses to the Rubber Hand Illusion in 23 adults with TS and 22 controls. Both TS and control participants reported equivalent subjective embodiment of the artificial hand: feelings of ownership, location, and agency were greater during synchronous visuo-tactile stimulation, compared to asynchronous. However, individuals with TS did not manifest greater proprioceptive drift, an objective marker of embodiment observed in controls. An 'embodiment prediction error' index of the difference between subjective embodiment and objective proprioceptive drift correlated with severity of premonitory sensations. Feelings of ownership also correlated with premonitory sensation severity, and feelings of agency with tic severity. These findings suggest that subjective bodily ownership, as measured by the rubber hand illusion, contributes to susceptibility to the premonitory sensations that may be a precipitating factor in tics.

Keywords: agency; body ownership; premonitory urge for tics scale (PUTS); proprioceptive drift; somatosensory; tics

1. Introduction

Tourette Syndrome (TS) is a neurodevelopmental disorder characterised by tics and premonitory sensations. Tics are repetitive, recurrent, movements and vocalisations, experienced as compulsive and ‘unvoluntary’ (Cavanna & Nani, 2013). Tics can often be preceded by premonitory urges or sensations, uncomfortable feelings of ‘itch’ or ‘pressure’, which may also be coupled to the location of the emerging tic. When these uncomfortable sensations occur, they are often relieved upon tic expression (Cavanna, Black, Hallett, & Voon, 2017). They have correspondingly been reported by some as antecedent factors to the generation of tics (Cavanna et al., 2017), although not all tics are preceded by premonitory sensations (Leckman, Walker, & Cohen, 1993), adding to the mystique of the role of subjective bodily perception in the expression of tics.

Alterations within motor networks likely underlie the expression of tics (Conceicao, Dias, Farinha, & Maia, 2017; Ganos, Roessner, & Munchau, 2013; Polyanska, Critchley, & Rae, 2017). However, neural systems supporting the representation of bodily sensations are also proposed to be dysfunctional in people with TS, reflected in the experience of premonitory urges (Cavanna et al., 2017; Conceicao et al., 2017). Somatosensory cortex, which underpins perception of touch, shows increased white matter connectivity and grey matter volume in people with TS. These alterations furthermore predict severity of both tics and premonitory sensations (Draganski et al., 2010; Thomalla et al., 2009). Insular cortex, which represents ‘interoceptive’ internal bodily states (Critchley & Harrison, 2013), also shows reduced cortical volume in TS, which correlates with severity of premonitory sensations (Draper, Jackson, Morgan, & Jackson, 2016). Functionally, both insula and somatosensory cortex are active immediately preceding tics (Bohlhalter et al., 2006; Neuner et al., 2014), indicating that both intero- and exteroceptive domains of bodily representation likely contribute to the symptoms of TS.

This burgeoning evidence for dysfunction within somatomotor neural systems supporting bodily representation in TS contrasts with relatively limited knowledge about the experience of bodily sensations, as measured using both objective and subjective indices: people with TS show lower interoceptive accuracy (Ganos et al., 2015), yet tend to report enhanced subjective sensitivity to internal bodily sensations such as heartbeats (Eddy, Rickards, & Cavanna, 2014). In exteroceptive somatosensory function, sensory thresholds for a variety of tactile, thermal, and pain stimuli are equivalent in adults with TS and controls (Schunke et al., 2016). Nevertheless, individuals with TS may report increased subjective sensitivity to touch stimuli (Belluscio, Jin, Watters, Lee, & Hallett, 2011). This suggests that people with

TS experience a mismatch between the perceptual experience of heightened somatosensory sensitivity, and quantitatively unaltered somatosensory function. It is possible, therefore, that neural circuitry underpinning heightened subjective bodily perceptions is the substrate for generating uncomfortable premonitory sensations that may play a role in the release of tics.

Furthermore, for some adolescents with TS, the expression of tics can be malleable with a corresponding reduction in severity with age (G. M. Jackson, Draper, Dyke, Pepes, & Jackson, 2015). However, it is not clear how plastic sensory representation and perception of the body is in TS. In healthy controls, under certain conditions, perceptual representation of the body is remarkably plastic: for example, in the rubber hand illusion, synchronous visual-tactile stimulation can induce feelings of ownership over an artificial (rubber) hand (Botvinick & Cohen, 1998). Yet plasticity in body perception has limits, highlighted by phantom limb patients in whom the sensation of an amputated limb lingers, despite no afferent input (Ramachandran & Hirstein, 1998). Neurodevelopmental lifespan factors, including age, can influence the plasticity of body perception. Such limited plasticity may reflect overly precise expectations around sensory experiences, leading to heightened subjective sensitivity to bodily feelings and thus premonitory sensations (Rae, Critchley, & Seth, 2018).

Here, we induced the rubber hand illusion in adults with TS and controls to explore the limits of plasticity in bodily perception in TS, and test the hypothesis that embodiment experiences during the rubber hand illusion are associated with symptom severity. We measured objective embodiment of the rubber hand using proprioceptive drift (Botvinick & Cohen, 1998), and subjective embodiment using self-report scales of ownership, location, and agency (Longo, Schuur, Kammers, Tsakiris, & Haggard, 2008).

Furthermore, proprioceptive drift and subjective ratings do not always correlate (Holle, McLatchie, Maurer, & Ward, 2011; Radziun & Ehrsson, 2018), and may relate to distinct aspects of embodiment (Rohde, Di Luca, & Ernst, 2011). This suggests that the rubber hand illusion may recalibrate spatial boundaries of internal body schema, or in self-location, without evoking subjective feelings of embodiment – or vice versa. When a mismatch occurs between actual and expected sensory experience, the discrepancy is termed ‘prediction error’. Such prediction errors may underlie aberrant experiences of selfhood in body illusions (Apps & Tsakiris, 2014). Therefore, to investigate whether discrepancies between objective (sensed) and subjective (predicted) dimensions of bodily perception underpin symptoms of TS, we computed an ‘embodiment prediction error’, to test if mismatch between

proprioceptive drift and subjective self-report of the rubber hand illusion predicted severity of premonitory sensations and tics.

2. Material and methods

2.1 Participants

Twenty-three adults with TS (13 male; age 18 to 51 years, mean 34 years; mean 14 years of education) and 22 controls with no history of neurological or psychiatric disorder (12 male; age 19 to 55 years, mean 34 years; mean 14 years of education) gave informed consent. TS participants were diagnosed by a UK neurologist or psychiatrist. Comorbid diagnoses of obsessive compulsive disorder (OCD) and attention deficit hyperactivity disorder (ADHD) were recorded. Seven participants with TS were taking serotonergic medications, two were taking dopaminergic, and one was taking both serotonergic and dopaminergic medications. The remaining thirteen were unmedicated.

Severity of tics, premonitory sensations, OCD symptoms, and ADHD symptoms were assessed with the Yale Global Tic Severity Scale (YGTSS; maximum 50); Premonitory Urge for Tics Scale (PUTS; maximum 36); Yale Brown Obsessive Compulsive Scale (YBOCS; maximum 40) and Adult ADHD Self-Report Scale (ASRS; maximum 6). See Table 1 for demographic and clinical details. The study was approved by the National Research Ethics Service South East Coast Brighton Research Ethics Committee, and all study procedures were carried out in accordance with the Declaration of Helsinki.

2.2 Rubber Hand Illusion

Participants sat opposite the experimenter and placed their hands inside a box, measuring 60cm (deep) by 84cm (wide) by 30cm (tall), with open sides, and covered by black cloth. A life-sized prosthetic right hand was placed with the index finger at the midline (i.e. 42cm from lateral edge of box). A coloured dot, placed 20cm to the right from midline, visible upon lifting the cloth, indicated where participants should place their right index finger. A hole in the box lid, measuring 20x20cm, permitted the participant to see the rubber hand, but not their own.

Participants underwent four testing blocks, two of synchronous visuo-tactile stimulation, and two asynchronous stimulation, in a randomised order. Each block started with a pre-stimulation baseline proprioceptive location rating of perceived own hand position. The experimenter placed a lid on the box, covering the viewing window, and a 100cm ruler at the rightward edge of the box. The participant was asked, "Using the values on the ruler, tell me where you feel your right index finger currently is". Three ratings were obtained, each with a different ruler offset, to minimise re-use of previous reports and ensure proprioceptive attention was focused on current perceived own hand position. The three offsets were selected randomly from a range comprising 0, 5, 10, 15, 20, and 25cm.

Following pre-stimulation proprioceptive location ratings, the experimenter removed the lid to reveal the viewing window, through which the participant could see the rubber hand. The induction phase of the block then began, in which the experimenter used two paintbrushes to stroke the index fingers of both the participant's hand, and the rubber hand. The surface area of the paintbrush bristles was 13mm wide and 13mm deep. Stroking was applied from the first knuckle to the tip of the finger, at a rate of 1Hz (i.e., one stroke per second). In synchronous blocks, the stroking was applied simultaneously from the knuckle to the tip on both hands. In asynchronous blocks, the stroking was offset by applying the brushes 180° out of phase between the two hands. Stroking proceeded for 90 seconds, during which the participant was asked to continue looking at the rubber hand.

After the induction phase, three post-stimulation proprioceptive location ratings were taken, in which the participant was asked to use the ruler to indicate, "Where do you feel your right index finger is now?". As with the pre-stimulation ratings, three ruler offsets, randomly selected from the same pre-stimulation range, were used, to prevent re-report of prior rating.

Following post-stimulation proprioceptive location ratings, the participant removed their hands from the box, and completed subjective embodiment ratings. These comprised 10 statements on which participants indicated their experience of rubber hand ownership (five items), location (three items), and agency (two items) on a 7-point Likert scale from -3 ('strongly disagree') to +3 ('strongly agree'), with 0 being 'neither agree nor disagree' (Longo et al., 2008) (see Table 2). The order of the 10 questions was randomised across the four blocks.

Proprioceptive drift for each block was calculated from the mean difference between the three pre- and three post-stimulation proprioceptive location ratings. Proprioceptive drifts were averaged across the two repeated synchronous and asynchronous blocks respectively. Subjective embodiment was calculated from mean ratings for the ownership, location, and agency statements, averaged across the two repeated synchronous and asynchronous blocks respectively.

2.3 Statistics

First, we assessed proprioceptive drift between the synchronous and asynchronous conditions, in participants with TS, and in controls, using repeated measures t-tests (SPSS version 24), to examine whether there was an effect of synchronous visuo-tactile stimulation in either group. Then, we tested whether the magnitude of this effect was different in TS, directly comparing the difference in proprioceptive drift between participants with TS and

controls using an independent measures t-test. We furthermore examined the interaction of synchronicity (within-subjects) and group (between-subjects) in a repeated measures ANOVA.

Subjective embodiment ratings are ordinal (rather than continuous), and furthermore, typically not normally distributed. Therefore, we assessed changes in (1) total, (2) ownership, (3) location, and (4) agency ratings between the synchronous and asynchronous conditions, in participants with TS and in controls, using non-parametric Wilcoxon signed-rank tests. Then, we tested whether these effects differed in TS, comparing the synchronicity difference in subjective embodiment ratings between participants with TS and controls using Mann-Whitney U-tests.

Regression analyses investigated whether objective (proprioceptive drift) and subjective (Likert ratings) measures of embodiment related to symptom severity. Synchronicity differences in proprioceptive drift and the three subjective embodiment ratings were entered as dependent variables; severity of tics (YGTSS), and premonitory sensations (PUTS), were independent variables. We further tested for (1-tailed) correlations between the rubber hand embodiment values, and symptom severity.

Finally, we examined 'embodiment prediction error': the degree of mismatch between subjective feelings of embodiment, and objective proprioceptive drift. We z-transformed the difference in (1) total subjective embodiment ratings, and (2) proprioceptive drift, between synchronous and asynchronous conditions. The z-scored total subjective embodiment, minus the z-scored proprioceptive drift, gave the embodiment prediction error (EPE). We examined whether EPE was different in participants with TS to controls using a Mann-Whitney U-test. To test whether EPE predicted severity of tics and premonitory sensations in TS participants, EPE was entered to a regression as the dependent variable, with YGTSS and PUTS as dependent variables; we further examined (1-tailed) correlations between these.

2.4 Data Availability

The anonymised raw data that support the findings of these study are available at the Open Science Framework [dataset] (Rae et al, 2018).

3. Results

3.1 Proprioceptive drift

Proprioceptive drift, an objective correlate of the rubber hand illusion, was greater in controls during synchronous (3.02cm) than asynchronous (0.29cm) stimulation ($t(21)=-2.818$, $p=0.010$; Figure 1a). Atypically, proprioceptive drift was attenuated in participants with TS, and was not significantly greater during synchronous (1.90cm) than asynchronous (0.59cm) stimulation ($t(22)=-1.620$, $p=0.120$; Figure 1a). Correspondingly, the numerical difference in proprioceptive drift across synchronous and asynchronous conditions was smaller in participants with TS (1.24cm) than controls (2.73cm), although this did not reach threshold statistical significance (direct comparison: ($t(43)=1.180$, $p=0.244$; Figure 1b; ANOVA stimulation x group interaction: ($F(43)=1.267$, $p=0.266$).

3.2 Subjective embodiment ratings

In controls, subjective induction of the rubber hand illusion during synchronous, but not asynchronous stimulation was supported by self-report measures: Total embodiment was greater during synchronous (-0.12) than asynchronous (-1.37) stimulation ($Z=-3.268$, $p<0.001$). On each of the three subscales; feelings of ownership (S: -0.07, A: -1.31; $Z=-3.175$, $p=0.001$); location (S: 0.09, A: -1.39; $Z=-3.605$, $p<0.001$); and agency (S: -0.57, A: -1.49; $Z=-2.330$, $p=0.017$); were greater during synchronous than asynchronous stimulation (Figure 2).

Similarly, in participants with TS, self-report measures confirmed subjective induction of the rubber hand illusion during synchronous compared to asynchronous stimulation: Total embodiment was greater during synchronous (-0.68) than asynchronous (-1.73) stimulation ($Z=-3.457$, $p<0.001$). On each of the three subscales; feelings of ownership (S: -0.64, A: -1.67; $Z=-3.100$, $p=0.001$); location (S: -0.64, A: -1.74; $Z=-3.736$, $p<0.001$); and agency (S: -0.85, A: -1.90; $Z=-3.630$, $p<0.001$); were greater during synchronous than asynchronous stimulation (Figure 2).

There were no significant group differences in subjective embodiment ratings across synchronous and asynchronous conditions between participants with TS and controls (Mann-Whitney U-tests for (1) total ratings, controls: 1.25, TS: 1.05; $U=234.000$, $p=0.673$; (2) ownership, controls: 1.24, TS: 1.02; $U=236.000$, $p=0.706$; (3) location, controls: 1.48, TS: 1.09; $U=209.000$, $p=0.323$, and (4) agency, controls: 0.92, TS 1.05; $U=243.500$, $p=0.833$). Thus, subjective feelings of embodiment increased with synchronous stimulation, in both controls and participants with TS.

3.3 Embodiment associations with symptom severity

Within the TS group, regression analysis with change in proprioceptive drift between synchronous and asynchronous conditions as a dependent variable, and YGTSS and PUTS as independent variables, was not significant ($F(2)=0.900$, $p=0.423$; no significant coefficients).

Subjective embodiment ratings showed significant relationships with symptoms: Regression analysis with change in ownership between synchronous and asynchronous conditions as a dependent variable, and YGTSS and PUTS as independent variables, was significant ($F(2)=4.082$, $p=0.033$; driven by PUTS: $B=0.116$, $t(22)=2.738$, $p=0.013$, with no significant effect of YGTSS: $B=-0.010$, $t(22)=-0.644$, $p=0.527$). PUTS correlated positively with change in ownership ($r=0.525$, $p=0.005$) (Figure 3a).

The second regression with change in location was not significant ($F(2)=1.740$, $p=0.201$; no significant coefficients), although there was a trend correlation with PUTS ($r=0.306$, $p=0.078$). The third regression with change in agency was not significant ($F(2)=2.156$, $p=0.142$; no significant coefficients). However, reported change in subjective agency correlated positively with YGTSS ($r=0.405$, $p=0.027$; Figure 3b), and with PUTS at trend significance ($r=0.300$, $p=0.082$).

3.4 Embodiment prediction error

Embodiment prediction error (EPE) represents the z-scored difference in total subjective embodiment with synchronous stimulation, minus the z-scored difference in proprioceptive drift.

Although numerically reversed, EPE was not significantly different in participants with TS (-0.24) to controls (0.25) (Mann-Whitney $U=197.000$, $p=0.204$; Figure 4a). However, EPE did relate to symptom severity in participants with TS: EPE correlated positively with PUTS ($r=0.364$, $p=0.044$), such that the greater the EPE, the greater the severity of premonitory sensations (Figure 4b; however multiple regression analysis with EPE as the dependent variable and YGTSS and PUTS as the independent variables did not attain threshold significance; $F(2)=1.526$, $p=0.242$).

4. Discussion

Uncomfortable premonitory sensations, which often precipitate the expression of tics, represent a key symptom of Tourette Syndrome (Cavanna et al., 2017). Altered bodily perception is also likely given structural differences in somatosensory regions (Draganski et al., 2010; Thomalla et al., 2009). Here, our findings support the notion that visuo-tactile integration of bodily perception is altered in TS, with patients less likely to experience proprioceptive changes in hand position during the rubber hand illusion than controls. Curiously, although participants with TS did not as strongly embody the rubber hand according to the objective measure of proprioceptive drift, both the TS and control groups showed subjective effects of rubber hand embodiment, rating feelings of ownership, location, and agency as greater under the synchronous visuo-tactile stimulation condition than asynchronous. As such, participants with TS tended to show a reversed 'embodiment prediction error' to controls, characterising a mismatch between subjective self-report and (reduced) proprioceptive drift. This discrepancy between subjective feelings of ownership and proprioceptive drift predicted severity of premonitory sensations in participants with TS. Furthermore, changes in ratings of ownership and agency with synchronous stimulation also predicted severity of premonitory sensations and tics, respectively.

These findings suggest that the strength of subjective bodily ownership, in the domain of visuo-tactile integration, may underpin sensitivity to the premonitory sensations that are often associated with tics. Furthermore, these results raise questions on how interactions between somatosensory neural pathways and other sensory and motor systems engender premonitory sensations and tics. Several factors may impact on bodily perception in TS, such as age-related plasticity, integration of intero- and exteroceptive sensations, and medications.

4.1 Plasticity of bodily perception in TS

The plastic potential of bodily perception is demonstrated in healthy controls by the rubber hand illusion, in which synchronous stroking of a visible rubber hand and the participant's unobserved own hand induces a sense of embodiment over the fake hand (Botvinick & Cohen, 1998). In some clinical populations, e.g. people with schizophrenia (Thakkar, Nichols, McIntosh, & Park, 2011), or delusional skin infestation (Eccles et al., 2015), there is an enhanced plasticity of body ownership, with greater proprioceptive drift towards the rubber hand than controls. In contrast, people with autistic spectrum conditions have a reduced susceptibility to the rubber hand illusion (Cascio, Foss-Feig, Burnette, Heacock, & Cosby, 2012; Paton, Hohwy, & Enticott, 2012), suggesting that clinical syndromes are

distributed along a spectrum of body ownership plasticity, arguably a proxy for the strength of self-representation (such as self/other distinction). Surprisingly, our data suggest that people with TS lie at the end of this spectrum where individuals are less implicitly susceptible to the rubber hand illusion, as indicated by lower proprioceptive drift.

In some populations, decreased distinction between the embodiment effects of synchronous and asynchronous stimulation indicates an enhanced propensity toward this illusion of body ownership, such as in ‘vicarious pain perceivers’ (Botan, Fan, Critchley, & Ward, 2018). This was not the case for the TS group, where proprioceptive drift was attenuated even for the synchronous condition. However, we tested adults with TS, in whom symptoms have remained or even worsened through adolescence: it is possible that a sub-group of younger TS participants, in whom tics reduce during neurodevelopment (G. M. Jackson et al., 2015), would show similar, or even enhanced, plasticity of bodily ownership relative to controls. This question is also pertinent to the plastic experience of premonitory sensations in TS, which are reported as becoming increasingly prevalent during childhood into adolescence (Banaschewski, Woerner, & Rothenberger, 2003).

In the context of generative models of human brain function, perceptual experiences, such as ownership of a limb, are defined by the combination of prior expectations and sensory evidence (Apps & Tsakiris, 2014). While greater embodiment of a rubber hand relative to controls, as in the case of schizophrenia, may indicate increased precision of visuo-tactile sensory inputs, reduced embodiment, as in the case of people with autistic spectrum conditions, and here, in TS, can be explained in terms of overly precise expectations of sensory experience (Rae et al., 2018). This would engender less susceptibility to synchronous visuo-tactile stimulation of a rubber hand.

4.2 Embodiment prediction error and susceptibility to premonitory sensations

Despite lower proprioceptive drift, participants with TS showed equivalent subjective self-reported embodiment during the illusion to controls. This mismatch mirrors similar findings in the domains of interoception and tactile perception, in which people with TS show either unaltered or even poorer sensory accuracy than controls, but report heightened subjective sensitivity (Belluscio et al., 2011; Eddy et al., 2014; Ganos et al., 2015; Schunke et al., 2016). Generative models account for such findings according to a mismatch in higher cortical areas between predictions and sensory evidence being ‘explained away’ as unpredicted sensations (Apps & Tsakiris, 2014). In TS, this may underlie the generation of premonitory sensations (Rae et al., 2018). Indeed, we found that both subjective ownership of the rubber hand, and the ‘embodiment prediction error’, quantifying the magnitude of

discrepancy between lesser (sensed) proprioceptive drift and greater subjective (predicted) embodiment, accounted for severity of premonitory sensations.

Although we did not investigate the neural processes underlying subjective embodiment in this study, neuroimaging investigations have identified somatosensory, insula, and premotor cortices as associated with experiencing the rubber hand illusion (Collins et al., 2017; Ehrsson, Holmes, & Passingham, 2005; Tsakiris, Hesse, Boy, Haggard, & Fink, 2007). These regions show structural and functional alterations in TS (Conceicao et al., 2017; Polyanska et al., 2017; Thomalla et al., 2009), which furthermore, predict premonitory sensation severity (Draganski et al., 2010; Draper et al., 2016). Together with our observation of embodiment prediction error in TS, these neural data highlight that an important future avenue is to more clearly elucidate how alterations in neural pathways for body perception underpin heightened sensitivity to bodily sensations and foster susceptibility to premonitory urges in TS.

A further question pertains to interactions between extero- and interoceptive sensory domains in TS. While somatosensory cortex represents sensations from the skin, which may be intimately tied to muscle locations at which tics are released, the insula represents visceral sensations, perhaps engendering uncomfortable internal bodily feeling states in the form of premonitory urges, which may then trigger mitigating tic actions (Conceicao et al., 2017; Rae et al., 2018). It is not yet clear how interactions between somatosensory and insular cortices underpin the symptoms of TS. However, in control participants, there are interoceptive influences on exteroceptive perception: a virtual rubber hand pulsing pink in synchrony with the participant's heartbeat induces greater proprioceptive drift and subjective embodiment ratings, and participants with higher interoceptive accuracy show the greatest effects (Suzuki, Garfinkel, Critchley, & Seth, 2013). Unmyelinated C-tactile fibres that carry signals arising from gentle stroke touch to the skin may mediate the tactile effect of the rubber hand illusion: these fibres are known to transmit activity to the insula (Olausson, Wessberg, Morrison, McGlone, & Vallbo, 2010). How the neural pathways subserving intero- and exteroceptive integration are altered in TS, and what this might mean for premonitory sensations, is yet to be elucidated.

4.3 Study limitations and future directions

In order to detail interactions amongst intero- and exteroceptive senses in TS, measures of exteroceptive function including tactile discrimination (Schunke et al., 2016) could be taken alongside a range of interoceptive measures beyond heartbeat sensations, such as respiration (Garfinkel et al., 2016), in the same sample. In addition, a greater understanding

of how embodiment – or reductions in embodiment, as seen here in lesser proprioceptive drift on the rubber hand illusion – relates to sensory cortex structure and function in TS can be achieved by combining such tests with neuroimaging.

A common feature of TS samples is patient heterogeneity, including multiple comorbidities and medication profiles (Cavanna, Servo, Monaco, & Robertson, 2009). Our mixed cohort of patients is representative of the TS population. However, some individuals were on dopaminergic or serotonergic medications, and some unmedicated. TS patients with comorbid ADHD may take stimulant medications, such as dexamphetamine, which increases dopaminergic transmission: in healthy controls dexamphetamine decreases proprioceptive drift, while feelings of subjective ownership are retained (Albrecht et al., 2011). This mirrors our findings in TS, indicating that intrinsic levels of dopaminergic neurotransmission may modulate embodiment experiences. It is plausible that in a TS sample in whom all were taking dopamine antagonists, effects of synchronous stimulation on proprioceptive drift would be reinstated to that of controls.

Furthermore, comorbidity status may influence embodiment effects, although to our knowledge tests of the rubber hand illusion are yet to be conducted on participants with exclusive diagnoses of OCD or ADHD.

In addition to medication and comorbidity status, experiences of premonitory sensations are also highly heterogeneous between individuals with TS, and within individuals over time and during neurodevelopment (Banaschewski et al., 2003; Leckman et al., 1993). Our findings suggest that this heterogeneity may relate to individual differences in embodiment. A priority for future work is to understand the multiple psychological and neural factors behind susceptibility to premonitory sensations, especially in light of their clinical relevance, with consistent associations between premonitory sensation experience, and both tic severity and patient quality of life (Crossley & Cavanna, 2013; Eddy & Cavanna, 2014; Reese et al., 2014). In addition, it remains important to disentangle the potential contribution of premonitory sensations to the generation of tics, and their increase in severity or conscious awareness during attempts at tic suppression (S. R. Jackson, Parkinson, Kim, Schuermann, & Eickhoff, 2011): it is possible that in both circumstances, subjective embodiment is one factor in individual patient susceptibility.

Finally, we note that although the TS participants did not show an effect of synchronous stimulation on proprioceptive drift, when formally comparing this to controls, either directly in a t-test or as an interaction, the group difference did not reach threshold significance. This

likely relates in part to sample size, and the within-group heterogeneity that is characteristic of TS: as such, group differences should be interpreted with caution, yet the relationship between subjective embodiment of the artificial hand and symptom severity is striking. In addition, while both groups showed highly significant changes in subjective ratings between synchronous and asynchronous stimulation, these tended to be from 'strongly disagree' to 'neither agree nor disagree', rather than a change to overt agreement. Nevertheless, the substantial changes in ratings indicate successful inducement of the rubber hand illusion, with significant impact on subjective embodiment of the artificial hand.

4.4 Conclusions

People with TS are less inducible on the rubber hand illusion, showing less proprioceptive drift with synchronous visuo-tactile stimulation. However, they report equivalent subjective embodiment of the rubber hand to controls. The extent of this subjective embodiment, and the mismatch with reduced proprioceptive drift, predicts premonitory sensation severity, suggesting that bodily perception plays a mediating role in TS symptom expression.

References

- Albrecht, M. A., Martin-Iverson, M. T., Price, G., Lee, J., Iyyalol, R., & Waters, F. (2011). Dexamphetamine effects on separate constructs in the rubber hand illusion test. *Psychopharmacology (Berl)*, 217(1), 39-50. doi:10.1007/s00213-011-2255-y
- Apps, M. A., & Tsakiris, M. (2014). The free-energy self: a predictive coding account of self-recognition. *Neurosci Biobehav Rev*, 41, 85-97. doi:10.1016/j.neubiorev.2013.01.029
- Banaschewski, T., Woerner, W., & Rothenberger, A. (2003). Premonitory sensory phenomena and suppressibility of tics in Tourette syndrome: developmental aspects in children and adolescents. *Dev Med Child Neurol*, 45(10), 700-703.
- Belluscio, B. A., Jin, L., Watters, V., Lee, T. H., & Hallett, M. (2011). Sensory sensitivity to external stimuli in Tourette syndrome patients. *Mov Disord*, 26(14), 2538-2543. doi:10.1002/mds.23977
- Bohlhalter, S., Goldfine, A., Matteson, S., Garraux, G., Hanakawa, T., Kansaku, K., . . . Hallett, M. (2006). Neural correlates of tic generation in Tourette syndrome: an event-related functional MRI study. *Brain*, 129(Pt 8), 2029-2037. doi:10.1093/brain/awl050
- Botan, V., Fan, S., Critchley, H., & Ward, J. (2018). Atypical susceptibility to the rubber hand illusion linked to sensory-localised vicarious pain perception. *Conscious Cogn*, 60, 62-71. doi:10.1016/j.concog.2018.02.010
- Botvinick, M., & Cohen, J. (1998). Rubber hands 'feel' touch that eyes see. *Nature*, 391(6669), 756. doi:10.1038/35784
- Cascio, C. J., Foss-Feig, J. H., Burnette, C. P., Heacock, J. L., & Cosby, A. A. (2012). The rubber hand illusion in children with autism spectrum disorders: delayed influence of combined tactile and visual input on proprioception. *Autism*, 16(4), 406-419. doi:10.1177/1362361311430404
- Cavanna, A. E., Black, K. J., Hallett, M., & Voon, V. (2017). Neurobiology of the Premonitory Urge in Tourette's Syndrome: Pathophysiology and Treatment Implications. *J Neuropsychiatry Clin Neurosci*, 29(2), 95-104. doi:10.1176/appi.neuropsych.16070141
- Cavanna, A. E., & Nani, A. (2013). Tourette syndrome and consciousness of action. *Tremor Other Hyperkinet Mov (N Y)*, 3. doi:10.7916/D8PV6J33
- Cavanna, A. E., Servo, S., Monaco, F., & Robertson, M. M. (2009). The behavioral spectrum of Gilles de la Tourette syndrome. *J Neuropsychiatry Clin Neurosci*, 21(1), 13-23. doi:10.1176/appi.neuropsych.21.1.13
- Collins, K. L., Guterstam, A., Cronin, J., Olson, J. D., Ehrsson, H. H., & Ojemann, J. G. (2017). Ownership of an artificial limb induced by electrical brain stimulation. *Proc Natl Acad Sci U S A*, 114(1), 166-171. doi:10.1073/pnas.1616305114
- Conceicao, V. A., Dias, A., Farinha, A. C., & Maia, T. V. (2017). Premonitory urges and tics in Tourette syndrome: computational mechanisms and neural correlates. *Current Opinion in Neurobiology*, 46, 187-199. doi:10.1016/j.conb.2017.08.009
- Critchley, H. D., & Harrison, N. A. (2013). Visceral influences on brain and behavior. *Neuron*, 77(4), 624-638. doi:10.1016/j.neuron.2013.02.008
- Crossley, E., & Cavanna, A. E. (2013). Sensory phenomena: clinical correlates and impact on quality of life in adult patients with Tourette syndrome. *Psychiatry Res*, 209(3), 705-710. doi:10.1016/j.psychres.2013.04.019
- Draganski, B., Martino, D., Cavanna, A. E., Hutton, C., Orth, M., Robertson, M. M., . . . Frackowiak, R. S. (2010). Multispectral brain morphometry in Tourette syndrome persisting into adulthood. *Brain*, 133(Pt 12), 3661-3675. doi:10.1093/brain/awq300
- Draper, A., Jackson, G. M., Morgan, P. S., & Jackson, S. R. (2016). Premonitory urges are associated with decreased grey matter thickness within the insula and sensorimotor cortex in young people with Tourette syndrome. *J Neuropsychol*, 10(1), 143-153. doi:10.1111/jnp.12089
- Eccles, J. A., Garfinkel, S. N., Harrison, N. A., Ward, J., Taylor, R. E., Bewley, A. P., & Critchley, H. D. (2015). Sensations of skin infestation linked to abnormal frontolimbic

- brain reactivity and differences in self-representation. *Neuropsychologia*, 77, 90-96. doi:10.1016/j.neuropsychologia.2015.08.006
- Eddy, C. M., & Cavanna, A. E. (2014). Premonitory Urges in Adults With Complicated and Uncomplicated Tourette Syndrome. *Behav Modif*, 38(2), 264-275. doi:10.1177/0145445513504432
- Eddy, C. M., Rickards, H. E., & Cavanna, A. E. (2014). Physiological Awareness Is Negatively Related to Inhibitory Functioning in Tourette Syndrome. *Behav Modif*, 38(2), 319-335. doi:10.1177/0145445513504431
- Ehrsson, H. H., Holmes, N. P., & Passingham, R. E. (2005). Touching a rubber hand: feeling of body ownership is associated with activity in multisensory brain areas. *J Neurosci*, 25(45), 10564-10573. doi:10.1523/JNEUROSCI.0800-05.2005
- Ganos, C., Garrido, A., Navalpotro-Gomez, I., Ricciardi, L., Martino, D., Edwards, M. J., . . . Bhatia, K. P. (2015). Premonitory urge to tic in Tourette's is associated with interoceptive awareness. *Movement Disorders*, 30(9), 1198-1202. doi:10.1002/mds.26228
- Ganos, C., Roessler, V., & Munchau, A. (2013). The functional anatomy of Gilles de la Tourette syndrome. *Neurosci Biobehav Rev*, 37(6), 1050-1062. doi:10.1016/j.neubiorev.2012.11.004
- S0149-7634(12)00194-7 [pii]
- Garfinkel, S. N., Manassei, M. F., Hamilton-Fletcher, G., In den Bosch, Y., Critchley, H. D., & Engels, M. (2016). Interoceptive dimensions across cardiac and respiratory axes. *Philos Trans R Soc Lond B Biol Sci*, 371(1708). doi:10.1098/rstb.2016.0014
- Holle, H., McLatchie, N., Maurer, S., & Ward, J. (2011). Proprioceptive drift without illusions of ownership for rotated hands in the "rubber hand illusion" paradigm. *Cogn Neurosci*, 2(3-4), 171-178. doi:10.1080/17588928.2011.603828
- Jackson, G. M., Draper, A., Dyke, K., Pepes, S. E., & Jackson, S. R. (2015). Inhibition, Disinhibition, and the Control of Action in Tourette Syndrome. *Trends in Cognitive Sciences*, 19(11), 655-665. doi:10.1016/j.tics.2015.08.006
- Jackson, S. R., Parkinson, A., Kim, S. Y., Schuermann, M., & Eickhoff, S. B. (2011). On the functional anatomy of the urge-for-action. *Cogn Neurosci*, 2(3-4), 227-243. doi:10.1080/17588928.2011.604717
- Leckman, J. F., Walker, D. E., & Cohen, D. J. (1993). Premonitory urges in Tourette's syndrome. *Am J Psychiatry*, 150(1), 98-102. doi:10.1176/ajp.150.1.98
- Longo, M. R., Schuur, F., Kammers, M. P., Tsakiris, M., & Haggard, P. (2008). What is embodiment? A psychometric approach. *Cognition*, 107(3), 978-998. doi:10.1016/j.cognition.2007.12.004
- Neuner, I., Werner, C. J., Arrubla, J., Stocker, T., Ehlen, C., Wegener, H. P., . . . Shah, N. J. (2014). Imaging the where and when of tic generation and resting state networks in adult Tourette patients. *Front Hum Neurosci*, 8, 362. doi:10.3389/fnhum.2014.00362
- Olausson, H., Wessberg, J., Morrison, I., McGlone, F., & Vallbo, A. (2010). The neurophysiology of unmyelinated tactile afferents. *Neurosci Biobehav Rev*, 34(2), 185-191. doi:10.1016/j.neubiorev.2008.09.011
- Paton, B., Hohwy, J., & Enticott, P. G. (2012). The rubber hand illusion reveals proprioceptive and sensorimotor differences in autism spectrum disorders. *J Autism Dev Disord*, 42(9), 1870-1883. doi:10.1007/s10803-011-1430-7
- Polyanska, L., Critchley, H. D., & Rae, C. L. (2017). Centrality of prefrontal and motor preparation cortices to Tourette Syndrome revealed by meta-analysis of task-based neuroimaging studies. *Neuroimage: Clinical*, 16, 257-267. doi:10.1016/j.nicl.2017.08.004
- Radziun, D., & Ehrsson, H. H. (2018). Short-term visual deprivation boosts the flexibility of body representation. *Sci Rep*, 8(1), 6284.
- Rae, C. L., Critchley, H. D., & Seth, A. K. (2018). A Bayesian account of tics. *Open Science Framework*. Retrieved from osf.io/c782a/
- Rae, C. L., Larsson, D., Eccles, J. A., Ward, J., Critchley, H.D. (2018). Subjective embodiment during the rubber hand illusion predicts severity of premonitory

- sensations and tics in Tourette Syndrome: dataset. *Open Science Framework*.
<https://osf.io/p96ch/>
- Ramachandran, V. S., & Hirstein, W. (1998). The perception of phantom limbs. The D. O. Hebb lecture. *Brain*, 121 (Pt 9), 1603-1630.
- Reese, H. E., Scahill, L., Peterson, A. L., Crowe, K., Woods, D. W., Piacentini, J., . . . Wilhelm, S. (2014). The premonitory urge to tic: measurement, characteristics, and correlates in older adolescents and adults. *Behav Ther*, 45(2), 177-186.
doi:10.1016/j.beth.2013.09.002
- Rohde, M., Di Luca, M., & Ernst, M. O. (2011). The Rubber Hand Illusion: feeling of ownership and proprioceptive drift do not go hand in hand. *PLoS One*, 6(6), e21659.
doi:10.1371/journal.pone.0021659
- Schunke, O., Grashorn, W., Kahl, U., Schottle, D., Haggard, P., Munchau, A., . . . Ganos, C. (2016). Quantitative Sensory Testing in adults with Tourette syndrome. *Parkinsonism Relat Disord*, 24, 132-136. doi:10.1016/j.parkreldis.2016.01.006
- Suzuki, K., Garfinkel, S. N., Critchley, H. D., & Seth, A. K. (2013). Multisensory integration across exteroceptive and interoceptive domains modulates self-experience in the rubber-hand illusion. *Neuropsychologia*, 51(13), 2909-2917.
doi:10.1016/j.neuropsychologia.2013.08.014
- Thakkar, K. N., Nichols, H. S., McIntosh, L. G., & Park, S. (2011). Disturbances in body ownership in schizophrenia: evidence from the rubber hand illusion and case study of a spontaneous out-of-body experience. *PLoS One*, 6(10), e27089.
doi:10.1371/journal.pone.0027089
- Thomalla, G., Siebner, H. R., Jonas, M., Baumer, T., Biermann-Ruben, K., Hummel, F., . . . Munchau, A. (2009). Structural changes in the somatosensory system correlate with tic severity in Gilles de la Tourette syndrome. *Brain*, 132(Pt 3), 765-777.
doi:10.1093/brain/awn339
- Tsakiris, M., Hesse, M. D., Boy, C., Haggard, P., & Fink, G. R. (2007). Neural signatures of body ownership: a sensory network for bodily self-consciousness. *Cereb Cortex*, 17(10), 2235-2244. doi:10.1093/cercor/bhl131

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Figures.

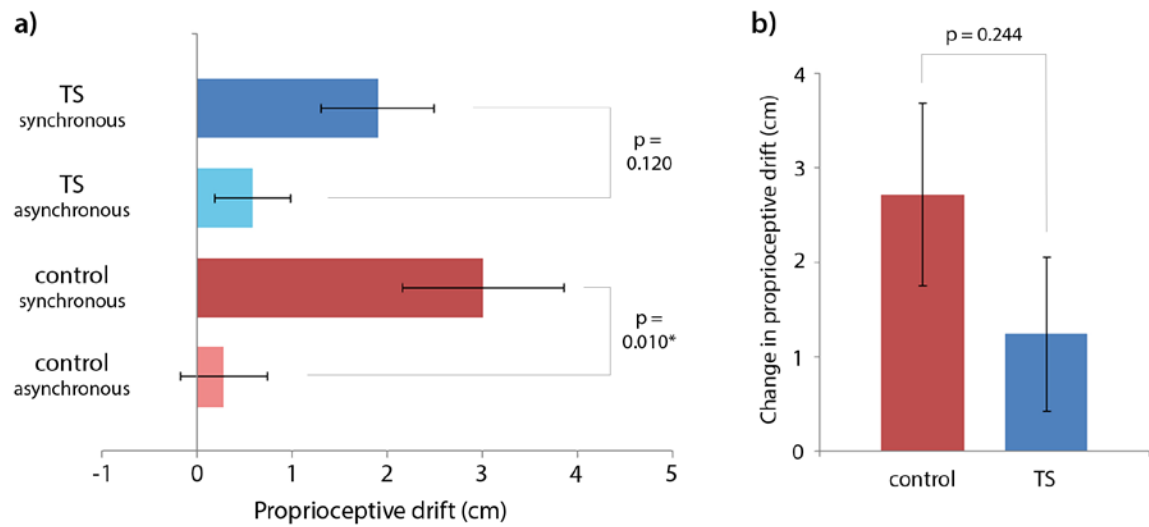


Figure 1. a) Proprioceptive drift during synchronous and asynchronous stimulation in participants with TS (dark blue, light blue) and controls (dark red, light red); b) difference in change in proprioceptive drift with synchronous stimulation between controls (2.73cm, red) and participants with TS (1.24cm, blue). *indicates significant at $p < 0.05$.

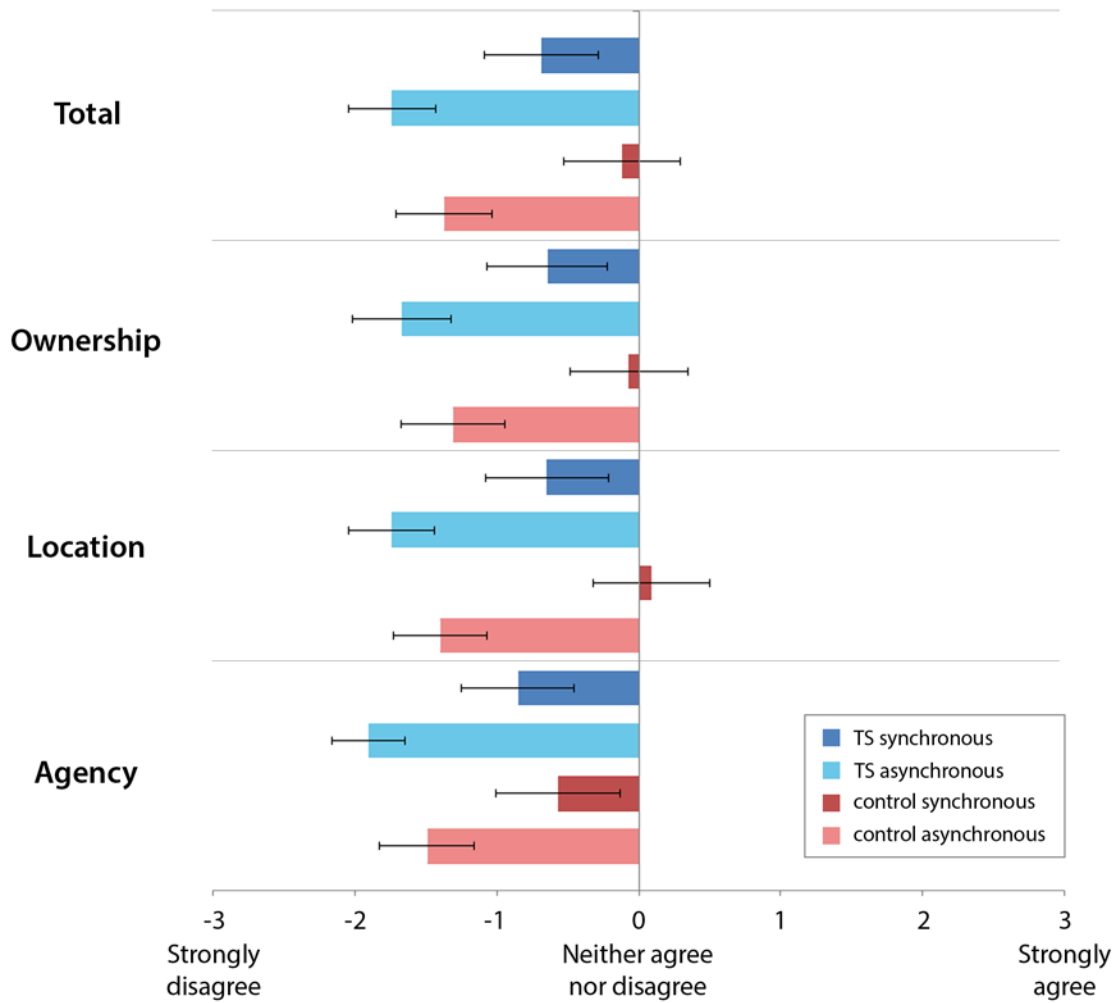


Figure 2. Subjective embodiment ratings during synchronous and asynchronous stimulation in participants with TS (dark blue, light blue) and controls (dark red, light red), for total ratings, and ownership, location, agency subscales. In both participants with TS and controls, subjective ratings were significantly greater during synchronous than asynchronous stimulation for all scales (see Results).

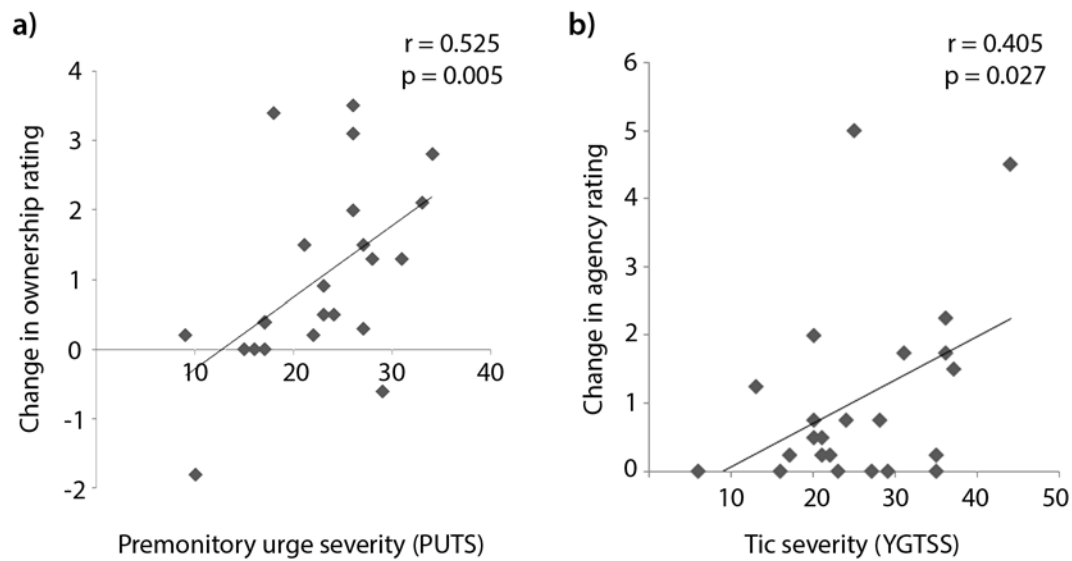


Figure 3. Correlations between change in subjective embodiment ratings with synchronous stimulation for a) ownership and premonitory sensation severity (PUTS), b) agency and tic severity (YGTSS).

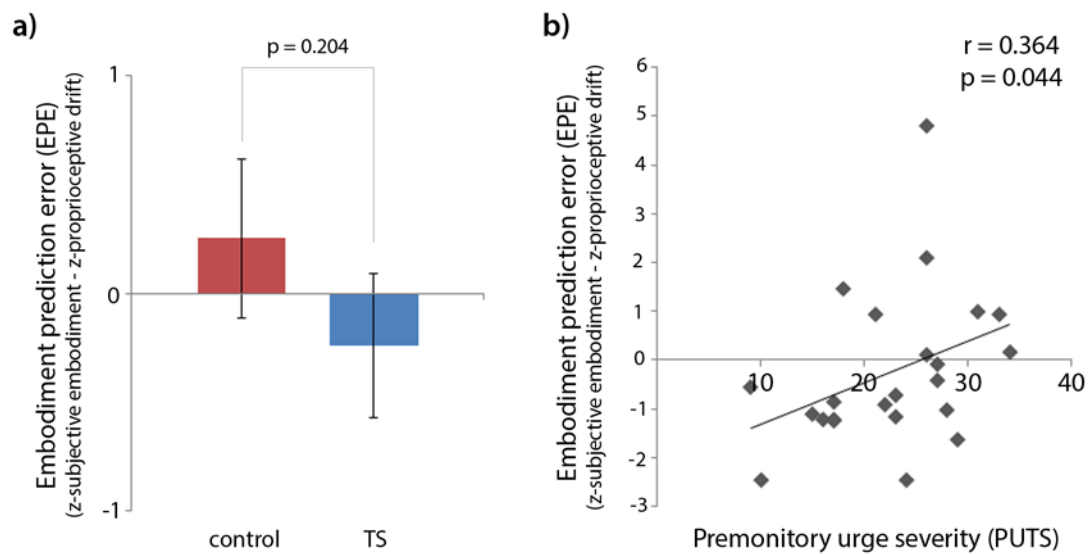


Figure 4. a) Embodiment prediction error (EPE; change in total subjective embodiment ratings minus change in proprioceptive drift) tends to be reversed in participants with TS (-0.24) compared to controls (0.25) but the difference is not statistically significant; b) Within TS participants, EPE predicts severity of premonitory sensations.

Tables.

	Participants with TS (n = 23)	Controls (n = 22)
Male / female	13 / 10	12 / 10
Age (years)	34 (18 – 51)	34 (19 – 55)
Years of education	14 (11 – 17)	14 (11 – 17)
YGTSS	25 (6 – 44)	-
PUTS	23 (9 – 34)	-
YBOCS	15 (0 – 32)	6 (0 – 20)
ASRS	4 (0 – 6)	1 (0 – 4)
Diagnosed OCD	9	-
Diagnosed ADHD	6	-

Table 1. Demographic and clinical features of participants. Values given as mean (range).

YGTSS = Yale Global Tic Severity Scale; PUTS = Premonitory Urge for Tics Scale; YBOCS = Yale Brown Obsessive Compulsive Scale; ASRS = Adult ADHD Self-Report Scale.

Dimension of subjective experience	Rating question
Ownership	It seemed I was looking directly at my own hand, rather than at a rubber hand.
Ownership	It seemed like the rubber hand began to resemble my real hand.
Ownership	It seemed like the rubber hand belonged to me.
Ownership	It seemed like the rubber hand was my hand.
Ownership	It seemed like the rubber hand was part of my body.
Location	It seemed like my hand was in the location where the rubber hand was.
Location	It seemed like the rubber hand was in the location where my hand was.
Location	It seemed like the touch I felt was caused by the paintbrush touching the rubber hand.
Agency	It seemed like I could have moved the rubber hand if I had wanted.
Agency	It seemed like I was in control of the rubber hand.

Table 2. The 10 rating judgements comprising the ownership, location, and agency dimensions of subjective rubber hand illusion experience (from Longo et al., 2008).